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Conducting an exercise trial in patients with early-onset dementia: Challenges faced and lessons learned

ASTRID M. HOOGHMISTRA^{1,2}, LAURA H.P. EGGERMONT¹, PHILIP SCHELTENS²,
WIESJE M. VAN DER FLIER^{2,3}, ROB J. VAN MARUM^{4,5}, JOS P.C.M. VAN CAMPEN⁶,
MATHIEU H.G. DE GREEF⁷, PETER A. KOPPE^{8†}, ERIK J.A. SCHERDER¹

Affiliations

¹ Department of Clinical Neuropsychology, VU University, Amsterdam, the Netherlands

² Alzheimer Center & Department of Neurology, VU University Medical Center, Neuroscience Campus Amsterdam, Amsterdam, the Netherlands

³ Department of Epidemiology & Biostatistics, VU University Medical Center, Amsterdam, the Netherlands

⁴ Department of Geriatrics, Jeroen Bosch Hospital, 's Hertogenbosch, the Netherlands

⁵ Department of General Practice & Elderly Care Medicine / EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam, the Netherlands

⁶ Department of Geriatrics, Slotervaart Hospital, Amsterdam, the Netherlands

⁷ Institute of Human Movement Sciences, University of Groningen, Groningen, the Netherlands

⁸ Department of Rehabilitation, Amstelland Hospital, Amstelveen, the Netherlands

Submitted

Abstract

Background/Aims: Epidemiological studies have shown a positive relationship between physical activity and cognition. Intervention studies examining the effects of physical activity on cognition in dementia show mixed results due to among others methodological difficulties. The present article discusses the challenges faced and lessons learned while conducting a randomized controlled trial (RCT) with exercise programs involving patients with early-onset dementia (EOD). The RCT aimed to investigate the effect of different exercise programs on cognition, activities of daily living and quality of life.

Methods: Description of the challenges faced and lessons learned during an RCT with three exercise intervention programs in patients with EOD.

Results: The main challenges faced were recruiting enough patients with EOD, logistics around the rehabilitation centers, and implementing tests for cognitive functions, in particular executive functioning.

Conclusions: Recommendations for future studies are to consider busy lifestyles of young patients, to create flexible intervention programs to match these lifestyles and to offer the programs as close to home as possible.

Introduction

Early-onset dementia (EOD), here defined as onset of symptoms before age 66, is an invalidating and fatal disease. When faced with the diagnosis in the midst of their lives, patients may be at the height of their career and may still have adolescent children.^{1,2} Patients with EOD ultimately become dependent on facilities that are in fact developed for elderly with dementia. There are hardly any facilities and interventions available that take into account the specific characteristics and needs of EOD patients.¹

A few pharmacologic intervention studies have focused specifically on younger patients with dementia.³⁻⁵ Non-pharmacological intervention studies, such as studies examining the effect of physical activity, have not included patients with EOD. This is unfortunate, for physical activity is increasingly recognized as being potentially beneficial for cognition. In individuals without dementia a physically active lifestyle in early or middle life reduces the risk of dementia later in life.⁶ Moreover, intervention trials have shown a beneficial effect of physical activity on cognition in persons at risk for dementia,⁷ patients with mild cognitive impairment (MCI),⁸ and patients with late onset dementia (LOD),⁹ although concerning the latter results are not consistent.¹⁰

Patients with EOD have symptoms that may lead to physical inactivity, such as loss of initiative and apathy.¹¹⁻¹⁴ These symptoms are more prevalent in EOD than in LOD.¹⁵ On the other hand, EOD patients suffer less from physical inconveniences than older populations,¹⁶ and hence are more capable to perform physical activity. With this in mind, we planned an RCT to study the effect of different intensities of exercise on cognition, activities of daily living, and quality of life in patients with EOD. The present paper provides a discussion of the challenges faced whilst conducting this RCT with patients with EOD. We will focus on the specific characteristics of this study, such as the population and the use of rehabilitation centers. The reasons for sharing our experiences are three-fold: 1) A publication bias exists towards publication

of positive studies. We believe it is useful to discuss studies that were not successful to balance this bias; 2) EOD patients are underrepresented in research when compared to LOD patients, which is unfortunate since the EOD population is a distinct group to study.^{12,17} During this study we have come to know motivations and choices of this patient group which we feel might benefit other researchers that plan to study this population; 3) Conducting exercise interventions in patients with a cognitive impairment posed some difficulty. Our experiences may benefit fellow researchers in the exercise field.

Study description

We conducted an RCT with three intervention arms. Two intervention programs were set in a rehabilitation center. The principle behind the rehabilitation part of this study was innovative: to rehabilitate patients in a rehabilitation center on the basis of a cognitive indication instead of a physical indication. Today, it is known that physical problems, such as gait disturbances, may present besides cognitive and behavioral problems in dementia.¹⁸ Treating patients in a rehabilitation center in small treatment groups instead of individually and in their own homes has advantages. Getting patients out of their homes three times a week for a longer period of time provides structure, and offers the opportunity to meet fellow EOD patients. The purpose of the aerobic program was to rehabilitate patients in order to maintain good physical functioning and to improve physical fitness, and hence influence cognitive functioning. The flexibility-relaxation program served as a control program. The program at home was based on the COACH program¹⁹ and made use of pedometers (OMRON Walking Style II). The principle behind this program was to increase intrinsic motivation to perform physical activity making use of exercise counselling.^{19,20} For a detailed description of the study protocol see.²¹ The medical ethical review committee of the VU University Medical Center (VUmc) approved the study in accordance with the Declaration of Helsinki (2008). This study is registered

in the Dutch trial design register (NTR2124). An overview of the study is provided in Table 1 (p. 138) and an flowchart in Figure 1 (p. 139).

Challenges encountered

RECRUITMENT

Recruitment took place primarily in the VUmc Alzheimer center in Amsterdam, the Netherlands. The VUmc Alzheimer center is a leading academic center in the dementia field worldwide and has a leading role in EOD in the Netherlands. Other centers that participated in the recruitment, were affiliated memory clinics in the Netherlands. Patients were recruited verbally and by information leaflets. Also, informal information meetings were held where patients were informed on the background and procedure of the study. The recruitment phase lasted 3 years. Approximately 250 patients were eligible and informed about the study. 53 patients in total were officially enrolled in the study (recruitment ratio 21%), of which 25 patients participated in the RCT part of the study, and 28 patients participated in the program at home.

CHALLENGE: RECRUITING PHYSICALLY INACTIVE PATIENTS

We intended to include primarily physically inactive patients. Physically inactive lifestyles are caused by apathy and executive function problems in EOD.^{13,14} A physically inactive lifestyle has negative effects on cognition.²² Also, it is thought that particularly physically inactive persons might benefit from an increase in physical activity.⁷ It turned out to be very difficult to motivate inactive patients to participate. Despite the support of the caregivers who often believed it would be beneficial for the patient to participate, the inactive patient was not willing to. The result was a physically active instead of a physically inactive study population. With physically active participants it is questionable whether an exercise intervention can pose additional effect on physical fitness, and hence on cognition.

CHALLENGE: BUSY LIFESTYLES OF YOUNG PATIENTS

A substantial part of the physically active patients was willing but unable to participate due to prioritizing. EOD patients (and caregivers) in early disease stages may still have active lifestyles. Some patients work (on a therapeutic basis) or they volunteer. Also, we experienced that patients wanted to enjoy their lives to the fullest by travelling or by spending time with their children. The intervention programs were set to take place on Mondays, Wednesdays, and Fridays, distributed through the week in order to create the best effect.²³ Days and times were fixed as space and man hours were hired. Also, the intervention period was lengthy with three months. This posed a problem for patients, for the intervention program interfered with their daily schedule. Several patients choose not to participate for this reason.

LESSONS LEARNED

- Physically inactive patients are particularly hard to motivate to participate in an exercise trial. Perhaps an external incentive could provide extra motivation to start, such as a financial compensation or a gift voucher. Once the patients are in training, internal motivation may grow.²⁰
- In our experience EOD patients have busy lifestyles. When planning an intervention study which is time consuming for the participant, it is advisable that the program is flexible and can be fitted into the lifestyle of the patient to enhance compliance.

RANDOMIZATION

Randomization was conducted after the baseline measurement. Randomization was applied for the two programs set in the rehabilitation centers and was provided blinded by an independent researcher. Block randomization with block size 4, i.e. 4 persons were randomized at once, was used to ensure an allocation ratio of 1:1 in the aerobic and in the flexibility-relaxation group. The program set at home was left out of the randomization because of difficulties with traveling (see below).

CHALLENGE: RCT SPLIT DUE TO TRAVEL DISTANCE

The study was originally designed as an RCT with three conditions and an allocation ratio of 1:1:1. However, travelling distance to and from the rehabilitation centers proved to be problematic and stressful for patients during a pilot study. Consequently, it was decided to split the trial in a two armed RCT and a separate program at home. Patients living within a 50 km radius of one of the rehabilitation centers were randomly assigned to one of the two programs there, patients living outside the 50 km radius were assigned to the program set at home.

CHALLENGE: EXPLAINING NECESSITY OF RANDOMIZATION

As in all RCTs patients favored one intervention program above the other.²⁴ Explaining the need of the randomization procedure is extra challenging with patients with dementia for they may not comprehend fully what is explained. Moreover, they may forget the relevance of the randomization, even when explanations are given multiple times and are provided in print. Our experience is that printed information leaflets were sometimes lost by the patient and had to be resent.

LESSONS LEARNED

- When planning an RCT there may be factors influencing the randomization that were not considered at first hand, a pilot period is essential. Procedures may be changed after the pilot to make the study more feasible.
- Information about important procedures of the study have to be given many times and in various ways when working with patients with dementia. It is advised to repeat explanation about the procedures at any new stage of the study both verbally and in print and to give them both to the patient and the caregiver.

INTERVENTION

Compliance was high in all three programmes (see Table 2, p. 140). The main reasons for not coming to the rehabilitation centers were vacation,

and not feeling well. Process evaluation (see Table 3, p. 141), making use of a 5-point Likert scale, showed that most patients and caregivers rated their participation as useful and pleasant. Also, meeting fellow participants was considered positive. Caregivers did not think that the participation of the patient was beneficial for their own lives.

CHALLENGE: REHABILITATION CENTERS

With the primary recruitment center in Amsterdam the researchers presumed that most EOD patients would live in the surroundings of Amsterdam. One rehabilitation center near Amsterdam was willing and able to participate (Amstelland hospital, Amstelveen, the Netherlands). However, it turned out that most of the patients diagnosed in the VUmc Alzheimer center were not living in or near Amsterdam. We tried to solve this by bringing patients to and from the rehabilitation centers with taxi's.

CHALLENGE: EXERCISE COUNSELING FOR PATIENTS WITH COGNITIVE DISORDERS

The program at home made use of pedometers in combination with exercise counseling, which has not been used before in patients with cognitive disorders.¹⁹ We have experienced that the therapeutic techniques applied in the exercise counseling may not be optimal for a population with dementia. During the exercise counseling cognitive techniques are used such as motivational interviewing and goal setting techniques. The caregiver was allowed to support the patient during the interviews, however a certain level of comprehension is required in order to attain motivation to perform the physical activity. Also, insight in the current level of physical activity is needed in order to discuss changing behaviours.

LESSONS LEARNED

- Rehabilitating patients with dementia in a rehabilitation setting has advantages, for example getting out of the house and contact with fellow sufferers. However participants should live as close to the rehabilitation centers as possible, because traveling can create stress.
- Exercise counseling may be too demanding for patients with EOD. Even with the support of caregivers the interviewing techniques proved difficult.

Perhaps a population with more subtle cognitive disorders, such as patients with MCI, may benefit more from the exercise counseling. Nonetheless, we found that the pedometer on its own increased motivation to walk. The feedback that the pedometer provides may work stimulating.

DATA-COLLECTION

Measurements took place at baseline, post intervention (after three months), and at follow-up (after six months). Measurements consisted of a neuropsychological examination followed by a week during which patients wore a pedometer and an actiwatch to measure activity levels. In the rehabilitation centers, participants received physical fitness measurements. Primary outcome measures were cognition (in particular executive functioning), activities of daily living, and quality of life.

CHALLENGE: MISSING DATA ON EXECUTIVE FUNCTIONING TESTS

Although our sample had a mild stage of dementia (mean Mini-Mental State Examination (MMSE)²⁵ over groups was 24.2 points) various patients were not able to perform the cognitive tests. In particular tests that assess executive functions such as mental flexibility and set shifting (Trail Making Test)²⁶ and response inhibition (Stroop Color Word Test)²⁷ proved to be difficult. Patients did not comprehend the instructions or were unable to complete the test in the allowed time frame. This created substantial missing data. Particular this type of missing data is problematic as the missing values are not random, and hence the data may not be representative of the EOD population. To replace these missing values with other values creates a bias in the data. Since we only had 9 valid scores in the aerobic group and 4 valid scores in the flexibility-relaxation group on these executive functioning tests on post measurement we decided not to analyze the intervention data.

LESSONS LEARNED

- Executive function tests are very complex tests. Patients in our study with mild stages of dementia had difficulty to perform them. Executive function

tests are useful in clinical practice. In clinical practice it is less problematic when the patient is not able to start or finish a test, because the observations why a patient is not able to complete the test are valuable. However, these qualitative observations are less relevant in research because it is hard to quantify them. Different outcome measures, such as proxy reports or objective devices that can be worn by the patient, may be more appropriate in intervention trials. In the present study these type of measures have proven to be attainable.

Conclusions

We discussed the challenges faced and lessons learned while conducting an RCT in which exercise programs were offered to patients with EOD. Sharing our experience with this specific population and topic may benefit future studies in this field and with this population. The most important learning points are summarized below.

- Because of their young age and busy lifestyles at time of disease onset EOD patients may choose not to participate in a lengthy intervention trial. This should be taken into consideration when conducting research with this population. An intervention program should be flexible and be implemented into the lives of the patients.
- In order to stimulate participation in a long intervention program, the intervention, and hence the rehabilitation center, should be as close to the patient as possible.
- Exercise counseling may be too challenging for patients with EOD because of cognitive impairments that limit abilities of comprehension and insight needed for motivational interviewing. However, using a simple device as a pedometer which provides feedback about the number of steps that

are taken may work motivating in itself. This may create opportunities for future research.

- Executive function tests may not be ideal for usage in studies with patients with EOD. The complex nature of these tests can create substantial missing data. It is recommended to consider different outcome measures to use besides cognitive tests, such as proxy reports to gain insight in the level of functioning and objective measurement devices that can be worn to gain insight in activity levels.

A cure for dementia being absent, studies investigating lifestyle factors that may be beneficial are encouraged. For EOD patients, it is advised to take the above mentioned considerations into account. In addition, studying the effect of exercise interventions may be better attainable when exercise is used as a preventative strategy in a population that has mild cognitive deficits but not yet dementia. Finally, although effect analyses were not possible in the present study, the patients rated their participation as pleasant and useful. Therefore, for EOD patients and persons with dementia in general, exercise can be considered a healthy and often highly valued activity to engage in.

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Table 1. Overview of the RCT

Methodological aspect	Description
Design	RCT with three intervention groups. Running from January 2010 until November 2012.
Sample	The sample size calculations showed that with power (1-beta) at .80 and alpha at .05 the required sample size was 120 participants in total. 250 patients were assessed for eligibility, 53 were enrolled in the study. Inclusion criteria were: Diagnosis of EOD, MMSE > 15, informal caregiver available. Informed consent was provided by the patient and the caregiver.
Setting	Recruitment took place in the Alzheimer center of the VUmc, and affiliated memory clinics. Interventions were set in two rehabilitation centers in the Netherlands: Amstelland Hospital, Amstelveen: n = 21 and Jeroen Bosch Hospital, 's Hertogenbosch: n = 4. The third program was set in participants' homes n = 28.
Randomization	Only for the programmes set in the rehabilitation centers. Block randomization (allocation ratio 1:1, block size 4). Randomization was provided by an independent researcher.
Intervention	Intervention activities in the rehabilitation centers ran for an hour, three times a week, for 12 weeks. Activities consisted of cycling on a ergometer (aerobic program) or flexibility and relaxation exercises (flexibility-relaxation program). The first and the last session were used to assess the physical fitness of the participants. The program at home made use of a pedometer, three exercise counseling sessions were held to provide support and motivation.
Data collection	Assessments were performed at baseline, post intervention (12 weeks) and at follow-up (24 weeks after baseline). Neuropsychological examinations endured 2 hours. Primary outcomes were: cognition (in particular executive functioning), activities of daily living, and quality of life.
Data analyses	Intention to treat analyses were planned, using the Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA).

Abbreviations: EOD: early-onset dementia; MMSE: Mini-Mental State Examination; VUmc: VU University Medical Center.

Figure 1. Flowchart

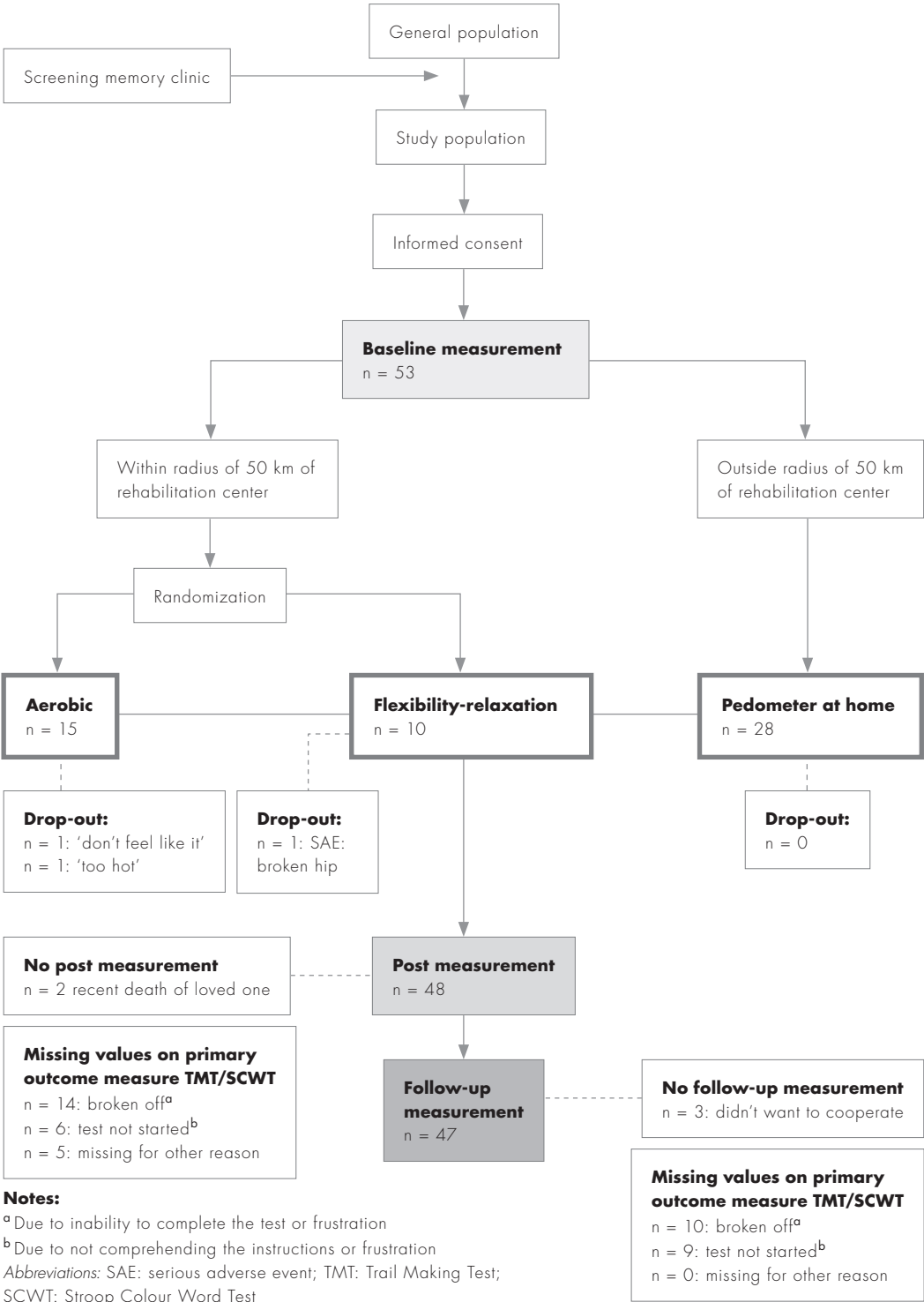


Table 2. Compliance and reasons for drop-out and not attending

	Rehabilitation center Aerobic <i>n</i> = 15	Rehabilitation center Flexibility-relaxation <i>n</i> = 10	At home <i>n</i> = 28
Compliance	91.5%	93.5%	n.a.
Dropout	2 ('don't feel like it', 'too hot')	0	n.a.
SAE	0	1 (hip broken)	n.a.
Reasons for not showing (# sessions) (%)			
Not feeling well	5 (13.9%)	6 (31.6%)	n.a.
Weather / traffic circumstances	2 (5.6%)	3 (15.8%)	n.a.
Vacation	19 (52.8%)	2 (10.5%)	n.a.
Too busy	0	1 (5.3%)	n.a.
Exploring psychogeriatric day care	0	1 (5.3%)	n.a.
Visiting dentist	0	1 (5.3%)	n.a.
Visiting physician	1 (2.8%)	0	n.a.
Partner absent	1 (2.8%)	1 (5.3%)	n.a.
Moving	1 (2.8%)	0	n.a.
Canceled without reason	7 (19.4%)	4 (21.1%)	n.a.
No cancellation	1 (2.8%)	0	n.a.

Abbreviations: n.a.: not applicable; SAE: serious adverse event

Table 3. Process evaluation of the three intervention programs

	Rehabilitation center Aerobic <i>n</i> = 11	Rehabilitation center Flexibility-relaxation <i>n</i> = 9	At home <i>n</i> = 23
Participants (# said yes) (%)			
Physically hard?	5 (45.5)	0	5 (21.7)
Fun?	11 (100)	8 (88.9)	21 (91.3)
Easy to keep up / sustain?	10 (90.9)	8 (88.9)	20 (87.0)
Useful?	9 (81.8)	7 (77.8)	20 (87.0)
Nice meeting fellow participants/caregivers?	11 (100)	9 (100)	n.a.
	<i>n</i> = 12	<i>n</i> = 8	<i>n</i> = 22
Caregivers (# said yes) (%)			
Participation of ... was positive?	10 (83.3)	8 (100)	18 (81.8)
Useful for participant?	11 (91.7)	7 (87.5)	17 (77.3)
Beneficial for own live?	4 (33.3)	4 (50.0)	7 (31.8)
Physically hard for participant?	4 (33.3)	1 (12.5)	3 (13.6)
Nice meeting fellow participants/caregivers?	8 (72.7) ^a	5 (71.4) ^a	n.a.

Note:

number of participants varies because of variation in the drop-out ratio. One caregiver did not accompany the participant to the rehabilitation center and did not answer this question.